ACUTE LEUKÆMIA IN ADULTS TREATED WITH 6-MERCAPTOPURINE

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THE ANALOGUES of the purine derivatives have taken their place beside the folic acid antagonists and the steroid hormones as useful agents in the treatment of acute leukæmia. The member of this group which has had the widest and most successful application is 6-mercaptopurine. It was synthesized by Elion, Burgi and Hitchings[1] at the Wellcome Research Laboratories and first used clinically by Burchenal *et al.*[2] Various reports[3-6] have appeared subsequently, including an extensive symposium[7] relating the results of a conference on 6-mercaptopurine held in December 1954 under the auspices of the New York Academy of Sciences. At that time reports were available on more than 186 cases occurring in adults and treated with the drug. The following relates our experiences with the use of 6-mercaptopurine in adults over the last two years.

Since October 1953 we have treated 29 cases of acute leukæmia with the drug alone or in combination. The youngest patient was 16 years old, the oldest 84. The age distribution is shown in Fig. 1. There were 13 females and 16 males. The interval between the onset of symptoms

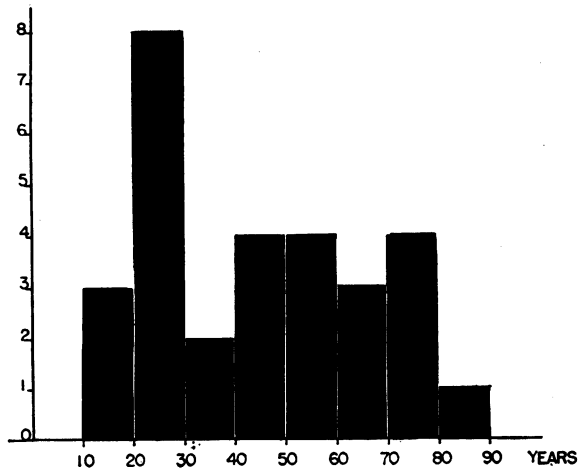

Fig. 1.—Age distribution of patients.

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referable to the leukæmia and the inception of treatment is shown in Fig. 2. It will be noted that in 17 the symptoms had existed for less

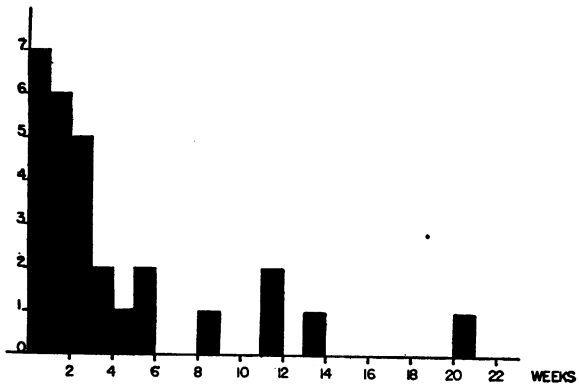

Fig. 2.—Interval between onset of symptoms and beginning of treatment.

than three months. A few had had symptoms for almost a year before a diagnosis was made. In two instances the patients were followed up for a year prior to a definitive diagnosis, with repeated blood and marrow examinations before blast cells finally appeared. One case was discovered incidentally when the patient was admitted for treatment of prostatic hypertrophy with retention.

The usual difficulties were experienced in categorizing the leukæmias with respect to cell type. Where transition had occurred between a chronic leukæmia and an acute process, the nature of the chronic was taken to indicate the nature of the acute. There were three cases of myeloblastic leukæmia following chronic granulocytic leukæmia and there was one case of lymphoblastic leukæmia following chronic lymphocytic leukæmia. One case of acute leukæmia occurred in a case of polycythæmia vera treated over a prolonged period with various agents including total body radiation and P^{32}. This case was presumed to be a myeloblastic leukæmia. Where an acute process was associated with large masses of tumour in lymph nodes, this was taken to be evidence of the presence of lymphoblastic leukæmia. There were seven such cases. In the remainder of the cases cellular morphology was the sole ground for differentiation. Six were considered to be myeloblastic and eight were classified only as blast cell leukæmias. No doubt these two groups included some cases which would have been designated as monocytic or monoblastic leuk-

æmia in other laboratories. There were two examples of reticulum cell leukæmia.

The aim of treatment was to improve the clinical state of the patient, render the circulating blood free of blast cells and other abnormal cells, and correct the anæmia and thrombocytopenia. Clinical improvement was considered complete if the patient returned to active business or household activities without symptoms; fair if he returned home to partial activity; and slight if bleeding stopped and general well-being improved but he was unable to leave hospital. Hæmatological remission was considered to be complete if anæmia was corrected without transfusion, platelet count returned to normal and blast cells disappeared from the circulating blood. Not enough serial bone marrow observations were made to know whether the complete remissions included a return to normal of the bone marrow picture. Hæmatological remission was considered to be partial if the total white count was reduced at the expense of the blast cells but recovery from anæmia or thrombocytopenia or both was partial or negligible.

The usual initial dose of 6-mercaptopurine was 150 mg. daily given in one dose by mouth in the morning. Alterations in dosage were made in agreement with hæmatological findings, an effort being made to achieve a constant maintenance dose sufficient to keep the proliferative activity of the blasts in check without producing thrombocytopenia or severe neutropenia.

RESULTS

Nineteen cases were treated with 6-mercaptopurine only for a period of 14 days, which was judged to be a sufficiently long period for assessment. The results are tabulated in Table I. Of the 10 who made no clinical response whatever, seven lived less than two weeks and died presumably before the drug could be thought to have its maximum effect.

Eight cases were treated with 6-mercaptopurine and adrenocorticotrophin (ACTH) or cortisone in combination. The results are set forth in Table II. The first case made two separate responses to 6-mercaptopurine, 27 weeks apart, each attended with thrombocytopenia which returned to normal when 6-mercaptopurine was stopped and cortisone substituted. The effect of the cortisone in this case is not clear-cut. The second case has had an excellent response. It is very difficult to separate the effects of 6-mercaptopurine and of cortisone, which she has been receiving continuously. Her spleen remains palpable and her platelet count, while not in the bleeding range, has not quite returned to normal. The third patient probably owes most of her remission to 6-mercaptopurine, although the clarity of the response was somewhat obscured by initial treatment with ACTH. In six of these cases the ACTH or cortisone was given because the platelet count was at an alarmingly low level, and there was a hæmorrhagic diathesis. The results of combined therapy do not permit a conclusion as to whether in those cases which improved the improvement was due to an alteration in the disease due to the 6-mercaptopurine or to an inhibition of bleeding due to the steroids with a stimulation of normal hæmatopoiesis.

TABLE I.

CASES TREATED WITH 6-MERCAPTOPURINE ALONE

Patient	*Clinical response*	*Hæmatological response*	*Duration of life weeks after onset of treatment*
E.R.	complete	complete	54 (still alive)
M.Br.	complete	complete	38 (still alive)
R.S.	complete	partial—a few blasts	22
V.A.	complete	partial—a few blasts	11
L.C.	fair	complete	16
J.K.	fair	partial	33
Y.C.	fair	partial	25
R.D.	fair	partial	18
A.O.	slight	partial	20
N.R.	slight	partial	15
G.B.	0	partial	2
D.C.	0	partial	8
V.M.	0	partial	2
M.Bi.	0	partial	5
A.M.	0	0	11
M.N.	0	0	1
R.G.	0	0	1
H.C.	0	0	2
M.T.	0	0	1
H.W.	0	0	1
R.O.	0	0	3 (still alive)

TABLE II.

CASES TREATED WITH 6-MERCAPTOPURINE AND ACTH OR CORTISONE

Patient	*Clinical response*	*Hæmatological response*	*Duration of life weeks after onset of treatment*
M.Ba.	complete	complete	33 (still alive)
D.F.	complete	partial	35 (still alive)
J.B.	complete	partial	19
D.K.	fair	partial	28
C.P.	fair	partial	13
J.L.	0	partial	17
W.S.	0	partial	2
A.G.	0	0	1

One case appeared to respond to 6-mercaptopurine after failing to do so to ACTH. One case, in which a slight apparent response to 6-mercaptopurine had gone on to escape from control, had a marked response of total white count and circulating blast cells but no clinical improvement after the administration of aminopterin. One patient treated with 6-mercaptopurine appeared to make an additional mild response when cortisone was added.

In those cases which showed hæmatological changes due to 6-mercaptopurine the change usually began to appear three to ten days after the onset of therapy and often achieved its maximum in 14 or 21 days. In two cases maximum response was delayed until about 50 days after the beginning of treatment. The total dose required to produce a maximal response varied from 700 mg. to 4,200 mg. and averaged about 2,000 mg. Total administered dosage depended in part, of course, on the duration of life. It reached 27.5 g. in one patient now dead, and has reached 16 g. in one survivor.

We have noted no clinical toxic effects which we could attribute to the drug as distinct from the disease. No skin lesions, gastrointestinal or nervous symptoms or other clinical signs or symptoms have been observed. Thrombocytopenia which developed during treatment and was relieved by stopping the drug or reducing the dose was noted in five patients. One of these showed the phenomenon on two separate occasions. Where the platelet count dropped to alarmingly low levels cortisone was administered. In two patients the daily dose of 6-mercaptopurine exceeded 150 mg. per day. One patient received 400 mg. per day for 10 days without enhanced effect. One received 250 mg. a day, also without added effect.

The correlation between type of cell and response to therapy is illustrated in Table III. It will be seen that the cases definitely recognizable as myeloblastic, because they followed chronic granulocytic leukæmia or polycythæmia, made the poorest response. Those with masses of lymphoid tissue did best as a group. Certain of the undifferentiated blast cell leukæmias, however, made excellent responses.

In general, those with total white counts in excess of 15,000 made a better response to treatment, both in regard to clinical and to hæmatological improvement. Only one failed to show some alteration of the total white count and in this case the dosage was probably inadequate.

TABLE III.

Type of leukæmia	*Patient*	*Clinical response*	*Hæmatological response*	*Duration of life—weeks after onset of therapy*
Myeloblastic following chronic granulocytic	Y.C.	fair	partial	25
	D.C.	0	0	8
	M.T.	0	0	1
Myeloblastic following polycythæmia vera	V.M.	0	partial	2
Myeloblastic	M.Ba.	complete	complete	33 (still alive)
	A.M.	0	0	11
	M.N.	0	0	1
	C.P.	fair	partial	13
	H.W.	0	0	1
	W.S	0	partial	2
Reticulum cell	A.G.	0	0	1
	J.K.	fair	partial	33
Lymphoblastic after chronic lymphocytic	J.L.	0	partial	17
Lymphoblastic with tumours in lymph nodes	M.Br.	complete	complete	38 (still alive)
	V.A.	complete	partial	11
	J.B.	complete	partial	19
	L.C.	fair	complete	16
	R.D.	fair	partial	18
	A.O.	slight	partial	20
	N.R.	slight	partial	15
	R.S.	complete	partial	22
Blast cell	M.B.	0	partial	5
	G.B.	0	partial	2
	H.C.	0	0	2
	R.G.	0	0	1
	D.K.	fair	partial	28
	D.F.	complete	partial	35 (still alive)
	R.O.	0	0	3 (still alive)
	E.R.	complete	complete	54 (still alive)

Of the 15 patients with clinical response of any degree, seven had no initial enlargement of lymph nodes. Of the remainder who had initial enlargement of lymph nodes, the nodes were unchanged in two, decreased in size in five, and had disappeared in one. There were five cases with no initial splenomegaly. Of the 10 initially enlarged spleens, four showed no change in size following treatment, two showed a decrease in size, and in four patients the spleen became no longer palpable. Those in whom the spleen showed the greatest regression received both 6-mercaptopurine and cortisone.

DISCUSSION

Acute leukæmia in adults is well known to present a difficult problem in therapy. Transfusions, antibiotics and other non-specific measures have only slight effect in altering the course of the disease. Antifolic acid agents, while effective in prolonging life in children, are disappointing in the adult and are attended with danger and discomfort from the toxic effects. ACTH and cortisone are also more effective in children than in adults; they have their greatest use in lymphoblastic proliferations and are less helpful in myeloblastic disease. In the latter they sometimes appear to aggravate the condition.[8]

6-Mercaptopurine appears to us to be more effective than either steroids or antifolic acid agents when used alone in adult acute leukæmia, even although, as these patients illustrated, it is only occasionally dramatically helpful. It has the advantage of being relatively non-toxic and does not add to the discomfort of the patient.

Combinations with antifolic acid drugs have not been used in this series except in one instance. Combination with steroids has sometimes assisted in the attack on the disease itself, and the steroids may control hæmolytic anæmia and may prevent hæmorrhage by direct effect on the vasculature at a time when the platelet count is low.

Where patients have survived for more than two weeks from the onset of treatment, they have almost always shown a reduction in total white cell count and in the number of circulating blast cells. This change has not always been accompanied by any improvement in the patient's clinical state. About half of all patients treated have shown some clinical response, ranging from slight to complete. The use of 6-mercaptopurine alone or in combination has produced in about one-quarter of the cases complete clinical remission ranging in duration from 3 to 12 months. This result is somewhat better than that reported by other authors for adult leukæmia.

SUMMARY AND CONCLUSIONS

1. Twenty-nine adults with acute leukæmia have been treated with 6-mercaptopurine alone or in combination.

2. The drug was used in daily doses of 150 mg. to begin with, and an effort was made to find a suitable maintenance dose.

3. No significant toxic effects were noted from the drug except depression of the platelet count.

4. Most of the patients who lived longer than two weeks showed a reduction in the total circulating white cell count and in the number of circulating blast cells.

5. About half of the treated cases showed a clinical response, and in half of these the response was complete and lasted for a variable period of from 3 to 12 months.

6. The addition of cortisone is sometimes helpful in influencing the course of the disease itself and in controlling hæmolytic anæmia or the hæmorrhage associated with thrombocytopenia.

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RÉSUMÉ

Un groupe de 29 malades adultes atteints de leucémie aiguë reçurent du 6-mercaptopurine seul ou en combinaison avec d'autres médicaments. Ce nouvel agent thérapeutique fut administré à raison de 150 mg. par jour comme dose d'attaque. On chercha à déterminer une dose de soutien convenable. La seule manifestation importante de toxicité fut une diminution du taux des plaquettes. La plupart des malades qui survécurent au delà de deux semaines subirent une diminution du nombre de leucocytes en général et de cellules primitives dans le sang périphérique. Environ la moitié des cas traités montrèrent une amélioration clinique et la moitié de ceux-ci s'améliorèrent d'une manière complète pour une période variant de 3 à 12 mois.

La cortisone peut quelquefois influencer favorablement le cours de la maladie, modifier l'anémie hémolytique ainsi que les manifestations hémorragiques résultant de la thrombocytopénie. M.R.D.

COSTOPHRENIC SEPTAL LINES IN PULMONARY VENOUS HYPERTENSION

One of the interesting and curious findings in roentgenograms of the thorax of patients with mitral heart disease has been the presence of fine, short, straight linear densities in the costophrenic regions. Although these lines are not specific for mitral heart disease, their preponderant presence in this condition stimulated a review of the roentgenograms at the Mayo Clinic of 152 surgical cases of mitral stenosis.

The lines with which this paper deals have been variously described as "lines B of Kerley", "horizontal lines", "linear x-ray shadows", and "septal lines". They are reported to occur occasionally in association with a number of conditions including acute and chronic pulmonary congestion, severe mitral stenosis, pulmonary hæmosiderosis in the absence of congestion, pneumoconiosis, diffuse pulmonary fibrosis and lymphogenous pulmonary metastasis. The lines usually are seen best in the costophrenic angles, and better on the right side than on the left. The posteroanterior view is the best, but occasionally an oblique or lateral view will show them to advantage. They run perpendicular to the pleural surface and vary in number from 2 or 3 to 10 or 15. They extend from 2 to 4 inches upward from the costophrenic angle and vary in thickness from a hairline to 2 mm. in diameter. Often they are spaced from 0.5 to 1 cm. apart. They may remain unchanged after mitral commissurotomy, or they may disappear.

There have been various interpretations of the pathogenesis of these lines, but most authors relate them to pulmonary hypertension. The investigations of these writers indicate that for practical purposes, these lines occur only among patients having pulmonary venous hypertension associated with pulmonary arterial hypertension, and particularly in mitral heart disease, but not in pulmonary hypertension confined to the pulmonary arterial side.

The authors consider that the finding of costophrenic septal lines on a roentgenogram is a valuable roentgenological sign strongly suggestive of mitral stenosis.—A. J. Bruwer, H. F. Ellis Jr., and J. W. Kirklin: *Circulation*, 12: 807, 1955.